

BIOGRAPHICAL SKETCH

NAME		POSITION TITLE	
Alexander Mark Papanastassiou MD		Assistant Professor of Neurosurgery	
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
Stanford University, Stanford, CA	B.A.S.	06/97	Biological Sci. and Music
University of California San Francisco, San Francisco, CA	M.D.	06/02	Medicine
Brigham and Women's Hospital/Harvard Internship, Boston, MA	Postdoctoral	06/03	General Surgery
Brigham and Women's Hospital/Children's Hospital Boston/Harvard Neurosurgery Residency, Boston, MA	Postdoctoral	06/09	Neurosurgery
Yale New Haven Hospital, New Haven, CT	Postdoctoral	06/10	Epilepsy Surgery

A. Personal Statement

The goal of the proposed research is to investigate epigenetic mechanisms contributing to Post-Traumatic Stress Disorder (PTSD) and explore whether electrical stimulation modulates these mechanisms. Our team has the research expertise to accomplish the proposed experiments, as well as the clinical expertise to consider these experiments in the development of stimulation as a therapy for patients with PTSD. As a medical student at UCSF, I performed neural recordings in the rat trigeminal nucleus to assess anti-nociceptive activity of cannabinoid compounds. As a post-doctoral fellow at MIT, I helped develop a high accuracy X-ray localization system and apply this for acquiring broad-scale spatial maps of visually selective neural responses in the macaque inferotemporal cortex. In parallel, I initiated a program for recording human electrocorticography responses in visually selective cortex with Gabriel Kreiman at Children's Hospital Boston and Brigham and Women's Hospital, studying robustness of object selectivity in spite of the presence of other images.

As an Assistant Professor of Neurosurgery at the University of Texas Health Sciences Center at San Antonio (UTHSCSA), where I specialize in stereotactic and functional neurosurgery, I have spent my initial time building a busy clinical program in epilepsy and functional neurosurgery for Parkinson's disease, essential tremor, dystonia, and obsessive-compulsive disorder. In parallel, I have developed an interest in PTSD from observing the clinical need for better treatments, and recognizing the well-developed network of PTSD researchers at UTHSCSA. UTHSCSA is the lead site for the STRONG STAR collaboration (South Texas Research Organizational Network Guiding Studies on Trauma and Resilience), a multidisciplinary, multi-institutional research consortium funded by U.S. Departments of Defense and Veterans Affairs to develop early interventions for the detection, prevention, diagnosis, and treatment of combat-related PTSD. Additionally, several labs at the institution are active in studying fear conditioning as it relates to PTSD and the stress response, as well as neurostimulation in animal models of psychiatric disorders. I have built a collaborative effort including members of the UTHSCSA PTSD community as well as Doug Williamson at Duke and Ann Rasmusson at Boston University to maximize the group's collective expertise. We believe this will optimize our experimental design and execution, with the goal of clinical translation in mind. As clinicians, we have specific plans for implementation, validation, and dissemination both for candidate biomarkers discovered in the proposed work, as well as for clinical trials of stimulation-based treatment for PTSD. We are collecting human data in parallel for discovery and validation of biomarkers. We are optimistic about the potential for neurostimulation to treat patients with PTSD, and believe a more complete mechanistic understanding will help guide pilot studies.

B. Positions and Honors**Employment**

2002-03	Intern in General Surgery, Brigham and Women's Hospital/Harvard University
2003-09	Resident in Neurosurgery, Brigham and Women's Hospital/Children's Hospital Boston/Harvard University
2009-10	Fellow in Epilepsy Surgery, Yale New Haven Hospital/Yale University
2010-Present	Assistant Professor, Department of Neurosurgery, University of Texas Health Science Center San Antonio

Honors

1993	David Starr Jordan Scholar, Stanford University
1997	B.A.S. with Distinction and Departmental Honors in Biological Sciences, Phi Beta Kappa
1998	French Foundation for Medical Research, Research Award
2000	Howard Hughes Medical Institute Medical Student Research Training Fellowship
2002	UCSF, M.D. with thesis
2012	S.A. Scene S.A. Doctors: Best of 2012
2013	S.A. Scene S.A. Doctors: Best of 2013
2014	S.A. Scene S.A. Doctors: Best of 2014
2015	Texas Monthly: 2015 Texas Rising Stars

C. Selected Peer-reviewed Publications

Papanastassiou A.M., Fields H.L., Meng I.D. Local application of the cannabinoid receptor agonist, WIN55,232-2, to spinal trigeminal nucleus caudalis differentially affects nociceptive and non-nociceptive neurons. *Pain*. 2004 Feb;107(3):267-75.

Josephson S.A., **Papanastassiou A.M.**, Berger M.S., Miller B.L., Geschwind M.D. The clinical spectrum and diagnostic utility of brain biopsy in patients with rapidly progressive neurologic conditions or dementia. *J Neurosurg*. 2007 Jan;106(1):72-5.

Dunn I.F., Agarwalla P.K., **Papanastassiou A.M.**, Butler W.E., Smith E.R. Multiple pilocytic astrocytomas of the cerebellum in a 17-year-old patient with Neurofibromatosis type I. *Childs Nerv Syst*. 2007 Oct;23(10):1191-4.

Papanastassiou A.M., Schwartz R.B., Friedlander R.F. Chiari I Malformation as a cause of trigeminal neuralgia. *Neurosurgery*. 2008 Sep;63(3):E614-5.

Cox D.D., **Papanastassiou A.M.**, Oreper D., Andken B.B., DiCarlo J.J. High-resolution three-dimensional microelectrode brain mapping using stereo microfocal X-ray imaging. *J Neurophysiol*. 2008 Nov;100(5):2966-76.

Op de Beeck H.O., DiCarlo J.J., Goense J.B.M., Grill-Spector K., **Papanastassiou A.M.**, Tanifuji M., Tsao D.Y. Fine-scale spatial organization of face and object selectivity in the temporal lobe: do functional magnetic resonance imaging, optical imaging, and electrophysiology agree? *J. Neurosci*. 2008 Nov;28:11796-11801.

Joshi A., **Papanastassiou A.M.**, Vives K.P., Spencer D.D., Staib L.H., Papademetris X. Light-sensitive visualization of multimodal data for neurosurgical applications. *Proc IEEE Int. Symp. Biomed. Imaging*. 2010 April 14-17;884-887.

Agam Y., Liu H., **Papanastassiou A.**, Buia C., Golby A.J., Madsen J.R., Kreiman G. Robust selectivity to two-object images in human visual cortex. *Curr Biol*. 2010 May;20(9):872-9.

Issa E.B., **Papanastassiou A.M.**, DiCarlo J.J. Large-scale, high-resolution neurophysiological maps underlying fMRI of macaque temporal lobe. *J Neurosci*. 2013;33(38):15207-19.

Mukundan L., Lie O.V., Leary L.D., **Papanastassiou A.M.**, Morgan L.C., Szabo A.C. Subdural electrode recording of generalized photoepileptic responses. *Epilepsy & Behavior Case Reports*. 2015;3:4-7.

Lie O.V., **Papanastassiou A.M.**, Cavazos J.E., Szabó C.Á. Influence of intracranial electrode density and spatial configuration on interictal spike localization: a case study. *J Clin Neurophysiol*. 2015 Jan 9. [Epub ahead of print].

D. Research Support (Current and Pending)

None

PROJECT SUMMARY

Traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are the signature illnesses of soldiers returning from recent wars in Iraq and Afghanistan. In the common scenario of exposure to a combat-related high explosive detonation, TBI may cause cognitive and mood symptoms overlapping with PTSD, and the interaction between these conditions is associated with greater disability. Approximately one third of PTSD patients are refractory to available therapies, resulting in a significant unmet treatment need. New targets for medicines and stimulation-related treatments are crucial. **We propose to test the novel hypothesis that *epigenetic modulation of the neuropeptide Y (NPY) system* plays a role in the pathophysiology of PTSD, and that amygdalar stimulation may relieve PTSD symptoms via *epigenetic modulation* of NPY.**

NPY is critical for attenuating the negative effects of exposure to serious threats in mammals. In combat-related PTSD, plasma and cerebrospinal fluid NPY is lower than in healthy controls. Higher plasma NPY levels are associated with recovery from PTSD over time, as well as better responses to Prolonged Exposure therapy, one of the current first-line treatments for PTSD. In the **predator scent model of PTSD**, where rats are exposed to feline urine, animals with resulting severe behavioral effects showed downregulation of NPY in the hippocampus, periaqueductal gray, and amygdala. Hippocampal NPY microinfusion attenuated the negative behavioral effects. We hypothesize that increased NPY promoter methylation in the amygdala, hippocampus, and peripheral blood will predict decreased NPY expression in this model. Blast injury produces mood and cognitive symptoms in humans and rodents that overlap with PTSD, and facilitates PTSD-like behaviors in the rat predator scent model. We hypothesize that blast injury potentiation of exposure to threat produces PTSD-like behaviors via NPY modulation, and that epigenetic modification of NPY underlies these effects.

In the proposed animal studies, rats will undergo behavioral testing before and after blast injury-potentiated predator scent exposure (**PSE**), followed by measurement of NPY promoter methylation, NPY mRNA, and NPY peptide levels in peripheral blood, amygdala, hippocampus, and infralimbic and prelimbic cortices. **In preliminary work, rats with PSE a) spend decreased time in the elevated plus maze open arm, signaling increased anxiety, and b) show low amygdalar NPY.** Therefore, increased NPY promoter methylation and decreased NPY mRNA and peptide are expected after blast exposure-potentiated PSE.

In a second set of experiments, rats will undergo right-sided or bilateral amygdalar stimulation after blast injury-potentiated PSE. **Preliminary data show increased mean time in the open arm of an elevated plus maze in association with bilateral stimulation compared to no stimulation after PSE.** NPY epigenetic modulation will be assessed. **Initial experiments show markedly increased NPY peptide levels with bilateral stimulation after PSE.** Stimulation is also expected to upregulate NPY after blast injury-potentiated PSE.

In the parallel set of proposed human studies, we plan to study epigenetic modulation of NPY in Soldiers before and after deployment in Operations Enduring Freedom, Iraqi Freedom, and New Dawn. 3,661 Soldiers completed PTSD and TBI health assessments, and underwent peripheral blood collection pre- and post-deployment. We will measure NPY promoter region DNA methylation, NPY mRNA, and NPY peptide levels in peripheral blood of 30 Soldiers each with PTSD, TBI from blast injury, neither or both, with epigenetic and molecular methodology described above. **Our data show increased PTSD symptoms after trauma exposure that are further elevated with TBI.** Soldiers with PTSD are expected to show increases in NPY promoter methylation and decreases in NPY mRNA and peptide levels across the deployment cycle, with greater effects with concomitant PTSD and blast injury from TBI.

Exploring how epigenetic control of NPY may contribute to both blast injury-potentiated PTSD pathophysiology is innovative, and may afford opportunities for development of novel treatments for PTSD, as well as biomarkers to guide treatment implementation in patients for whom they are most likely to be successful.